DEPARTMENT OF HEALTH & HUMAN SERVICES

HFI-35 g3014d

Food and Drug Administration
Detroit District
1560 East Jefferson Avenue
Detroit, MI 48207-3179
Telephone: 313-226-6260

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

WARNING LETTER
2002-DT-18

January 9, 2002

Jerome W. Mincy
President and CEO
Opti-Med Controlled Release Labs, Inc.
120 E. Third Street
Seymour, Indiana 47274

Dear Mr. Mincy:

A September 26 through October 15, 2001 inspection of your drug manufacturing operations found that your firm is operating in serious violation of the Federal Food, Drug, and Cosmetic Act (the Act). During the inspection, our investigator documented numerous significant deviations from the Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Part 211), which cause your prescription drug products, (Vitamins and/or Minerals with Folic Acid, and Novasal Analgesic, Anti-Inflammatory Pain Tablets, and Ed-Flex Capsules) to be adulterated within the meaning of section 501(a)(2)(B) of the Act. While examples are as follows, we suggest you refer to the list of inspectional observations [the FDA-483] which was issued at the conclusion of the inspection for additional details:

1. Failure to have a quality control unit adequate to perform its functions and responsibilities, as required by 21 CFR 211.22. Your failure to have an adequate quality control unit is demonstrated by the number and types of inspectional observations made during this inspection. For example, 483 observations 1 and 3.

2. Failure to establish and to follow validated written control procedures for production and process control designed to assure batch uniformity and the integrity of drug products, as required by 21 CFR 211.100 For example, 483 observations 2(a-l).

3. Failure to perform sampling and testing of in-process materials and drug products to assure batch uniformity and homogeneity as required by 21 CFR 211.110(a)(3). For example, see 483 Observation 18.

4. Failure of the quality control unit to review all drug product production and control records to determine compliance with established written procedures before a batch is released or rejected, and to perform an investigation when a batch or its components fails to meet specifications, as required by 21 CFR 211.192. For example, 483 observations 13,21,22,24,25 and 28.

5. Failure to have batch production and control records that include complete information relating to the production and control of each batch, as required by 21 CFR 211.188. For example, 483 observations 19,20 and 23.

6. Failure to have, to follow, and to have a record justifying any deviations from procedures for production and process control designed to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess, as required by 21 CFR 211.100(b). For example, 483 observation 1(g).

7. Failure to make an appropriate laboratory determination of satisfactory conformance of each batch of drug product to its final specifications prior to its release, as required by 21 CFR 211.165. For example, 483 observation 2(c).

8. Failure to maintain laboratory records that include complete data from all tests necessary to assure compliance with established specifications and standards, as required by 21 CFR 211.194. For example, 483 observations 2(h) and 2(j).

9. Failure to establish specifications for those products received and used in your repackaging operations to include a physical description for comparison to establish that the identity agrees with that in the certificate of analysis, as required by 21 CFR 211.84. For example see 483 observation 14.

10. Failure to establish component specifications for some ingredients used in the manufacturing of drug products as required by 21 CFR 211.84. For example see 483 observation 15.

11. Failure to hold under a quarantine system, all drug component ingredients until all specified acceptance testing has been completed as required by 21 CFR 211.82(b). For example, see 483 observation 16.

12. Failure to perform the identification test separately on each of the samples collected from separate containers of bulk drug ingredients as required by 21 CFR 211.84(d). For example see 483 observation 17.

13. Failure to adequately evaluate, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing and control procedures, as required by 21 CFR 211.180(e). For example, see 483 observation 29.

14. Failure to have, and to follow, a stability testing program adequate to assess the stability characteristics of drug products, as required by 21 CFR 211.166. For example, see 483 observations 4,5,6 and 7.

15. Failure to assure that equipment is routinely maintained and cleaned according to a written program designed to assure proper performance, as required by 21 CFR 211.67. For example, see 483 observation 8.

16. Failure to evaluate and establish specifications for the building HVAC system, to provide for periodic checks to assure the system provides proper air flow, humidity, and temperature, and to establish a preventative maintenance program for the HVAC system as required by 21 CFR 211.46, and 21 CFR 211.58. For examples, see 483 observations 9,10 and 11.

17. Failure to establish and follow equipment cleaning validation procedures designed to assure appropriate cleaning procedures are in place as required by 21 CFR 211.67. For example, see 483 observation 12.

18. Failure to provide for employee training on a continuing basis to assure their knowledge and understanding of the drug CGMP regulations as required by 21 CFR 211.25. For example, see 483 observation 26.

19. Failure to establish a complete label accountability procedure to include the specific method or methods to be used to perform label counting as required by 21 CFR 211.184. For example, see 483 observation 27.

We acknowledge your October 23, 2001 response to the list of inspectional observations, and your commitments to take steps to correct the noted violations. Our review of your responses finds some appear to only address the specific examples noted on the FDA-483. We are not sure from these responses that you understand all of the specific and/or systemic deficiencies which may exist at your firm. For example:

FDA-483 Observation 2(b)
Your response suggests you consider process validation to be a test to confirm a batch process is in control and that three samples from the batch is adequate. We consider process validation to be an evaluation of the process to determine the optimum parameters to assure blend uniformity by testing a larger number of samples taken at various times during the blending operation from several locations in the blender. Once this validation is completed on a minimum of three batches, control limits for subsequent batches can be set based upon the data.

FDA-483 Observation 2(c)
Your response indicates you believe analysis of a single ingredient (copper) from the vitamin pre-mix is adequate to validate the blend uniformity for Cenogen OB Capsules. The observation states the process validation did not include testing for the critical ingredient Folic Acid. The Folic Acid is not part of the vitamin pre-mix, and it was added in a separate step, therefore it must be subject to a specific analysis during both process validation studies as well as batch to batch control testing.

FDA-483 Observation 2(l)
Your response indicates you have taken the procedures or product master records from other manufacturers and begun producing these products in a different facility, with different equipment and control procedures. The records do not demonstrate any validation study to determine optimum parameters for blending, compressing, and capsule filling, and no effort to vary the process to demonstrate the robustness of the established process.

FDA-483 Observation 17
Your response questions the logic of performing separate identity tests on a sample from each sampled container of incoming bulk drug components. When multiple containers of a drug ingredient are sampled, according to a logical sampling plan, the identity test should be performed on each sample. The assay test can then be performed once on a composite of those samples. The ID test provides increased assurance that each container is in fact the correct product. A single container of the wrong product, included in a composite sample, may not be revealed by the assay of that composite sample.

FDA-483 Observation 18
You question the need for Blend Uniformity Analysis (BUA). Your Folic Acid containing drugs are subject to the USP monograph that calls for content uniformity testing of Folic Acid Tablets. The requirements of 21 CFR 211.110 call for appropriate sampling of in-process and finished drugs to assure uniformity of the batch. The deficiencies in your process validation studies listed under FDA-483 Observation 2., includes item 2(c) the lack of uniformity testing for the critical ingredient Folic Acid. Your failure to perform any folic acid testing, concerns us that the most significant active ingredient in these drugs is not subject to any analytical control testing.

We suggest that you thoroughly evaluate the adequacy of your procedures and controls, and that you take whatever actions are necessary to make systemic corrections and to assure that similar violations will not recur. The above list of deviations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Good Manufacturing Practice Regulations. Other Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. Additionally, pending NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

We request that you take prompt action to correct these violations. Failure to promptly correct these violations may result in enforcement action being initiated by the Food and Drug Administration without further notice, such as seizure and/or injunction.

Please notify this office in writing, within fifteen (15) working days of receipt of this letter, as to any additional steps you have taken to correct these violations, including an explanation of each step being taken to identify and make corrections to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time frame within which the corrections will be implemented.

Your reply should be directed to Melvin O. Robinson, Compliance Officer, at the above address.

Sincerely,

Joann M. Givens
District Director
Detroit District